REVERSE-IT
Rapid and SustainEd ReVERSal of TicagrElor - Intervention Trial

REVERSE-IT:

Effect of Bentracimab on Platelet Inhibition and Hemostasis in Patients on Ticagrelor with Major Bleeding or Requiring Urgent Procedures

Deepak L. Bhatt, MD, MPH, Charles V. Pollack, Jr., MD, C. David Mazer, MD, Dominick J. Angiolillo, MD, PhD, Ph. Gabriel Steg, MD, Stefan K. James, MD, PhD, Jeffrey I. Weitz, MD, Rohit Ramnath, PhD, Susan E. Arnold, PhD, Michael C. Mays, BS, Bret R. Umstead, MS, Barbara White, MD, Lisa L. Hickey, MS, Lisa K. Jennings, PhD, Benjamin J. Curry, PhD, John S. Lee MD, PhD, Subodh Verma, MD, PhD, on Behalf of the REVERSE-IT Investigators

Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Novartis, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); **Research Funding**: Abbott, Afimmune, Amarin, Amgen, **AstraZeneca**, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Lexicon, Lilly, Medtronic, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, **PhaseBio**, PLx Pharma, Regeneron, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, 89Bio; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Philips, Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Takeda.

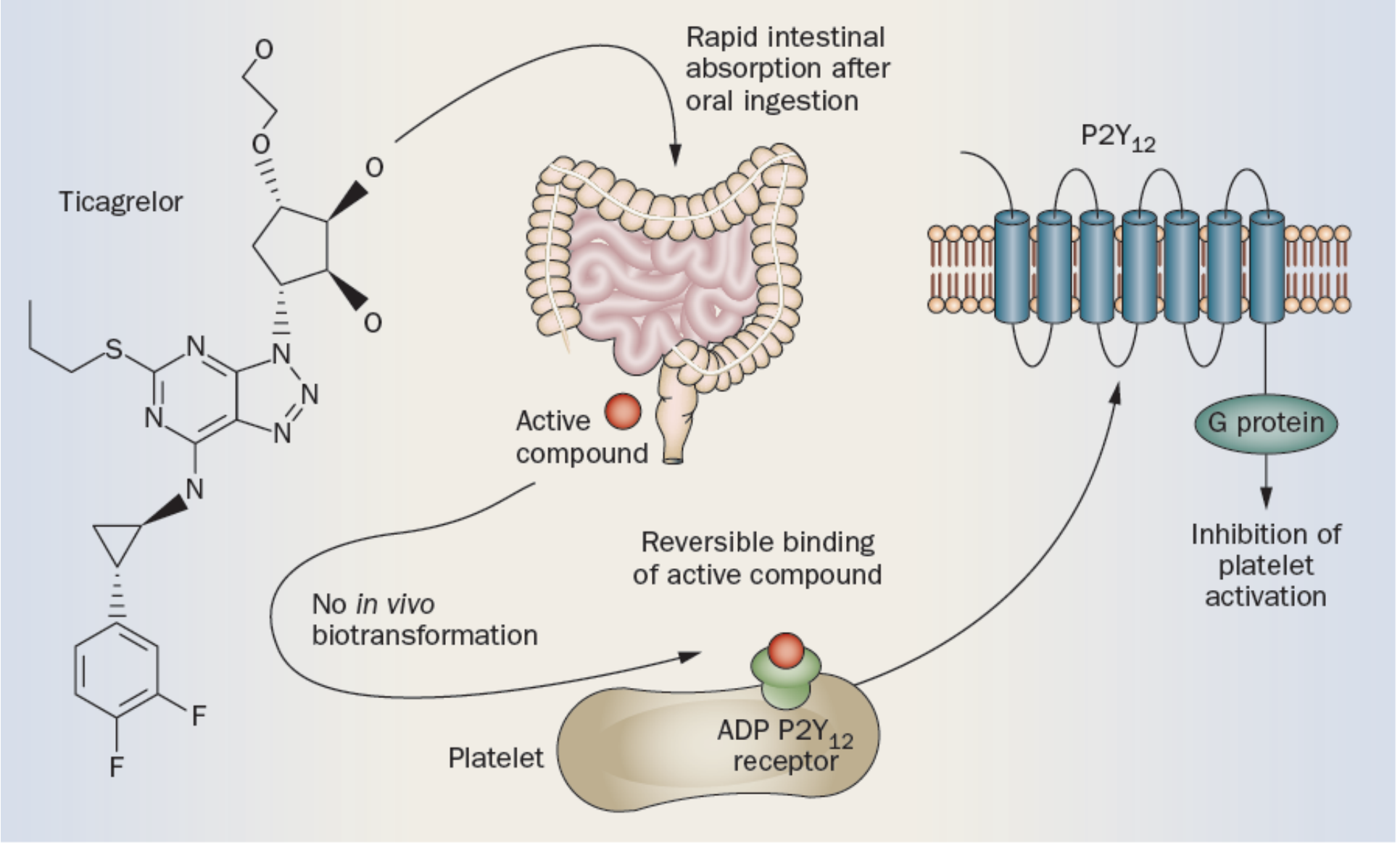
REVERSE-IT is funded by PhaseBio. This presentation discusses off label and investigational uses of drugs.

Ticagrelor: Substantial Data, with Broad Label

- Ticagrelor is an oral $P2Y_{12}$ inhibitor that is effective (and FDA-approved) in patients with acute coronary syndromes, prior myocardial infarction, high-risk coronary artery disease, transient ischemic attack, and stroke, based on PLATO,[1,2] PEGASUS,[3,4] THEMIS,[5,6] THEMIS-PCI,[5,7] and THALES.[8]
- As with other antiplatelet drugs, spontaneous major bleeding and bleeding associated with urgent or emergent invasive procedures are concerns.
- The antiplatelet effects of ticagrelor cannot be reversed with platelet transfusion. Therefore, a rapid-acting reversal agent would be useful.

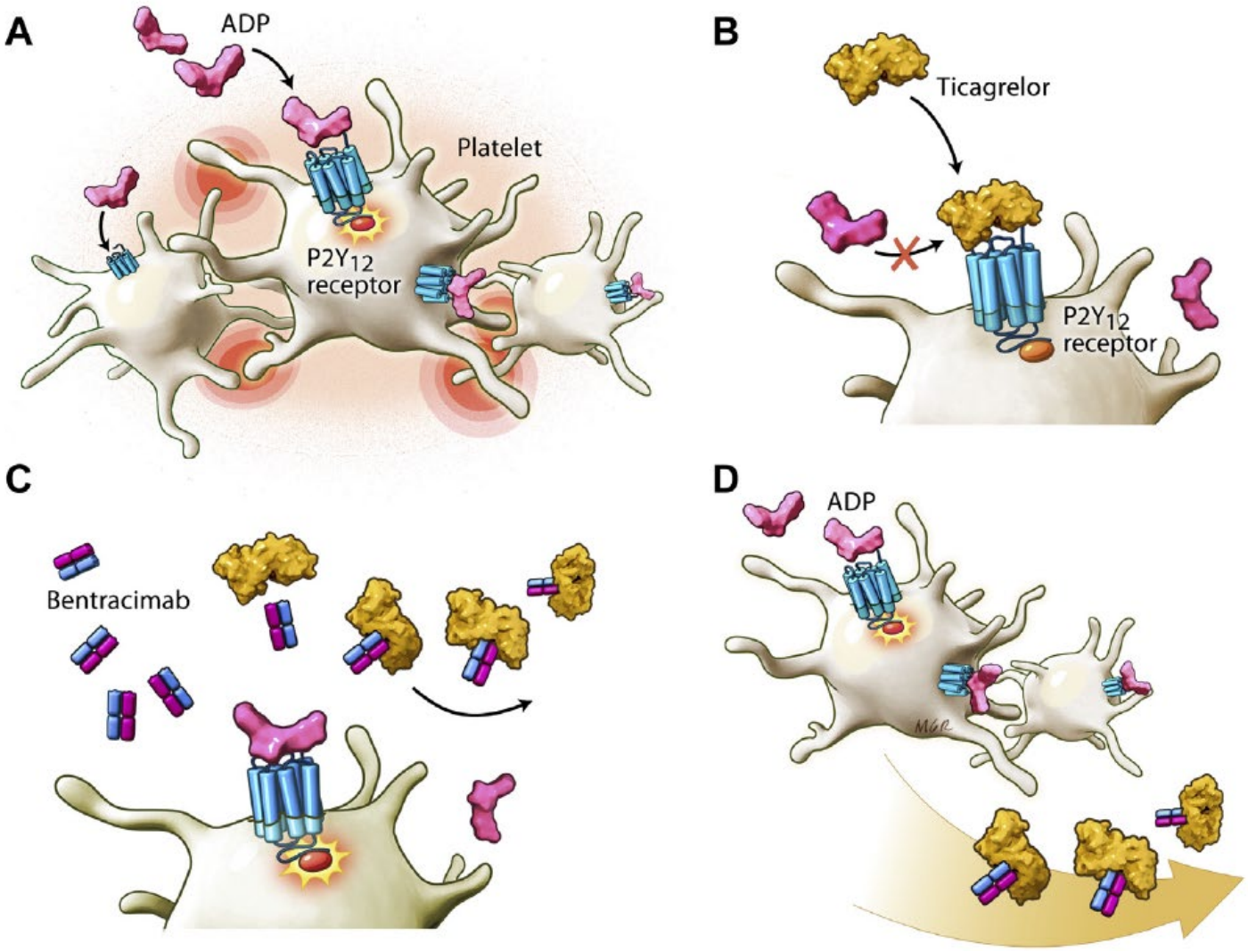
[1]James S, Akerblom A, Cannon CP, et al. *Am Heart J*. 2009;157:599-605.
[2]Wallentin L, Becker RC, Budaj A, et al. *N Engl J Med.* 2009;361:1045-57.
[3]Bonaca MP, Bhatt DL, Braunwald E, et al. *Am Heart J*. 2014;167:437-44.
[4]Bonaca MP, Bhatt DL, Cohen M, et al. *N Engl J Med*. 2015;372:1791-800.
[5]Bhatt DL, Steg PG, et al. *Clinical Cardiology* 2019; 42: 498-505.
[6]Steg PG, Bhatt DL, et al. *N Engl J Med.* 2019;381:1309-1320.
[7]Bhatt DL, Steg PG, et al. *Lancet*. 2019;394:1169-1180.
[8]Johnston SC, Amarenco P, et al. *N Engl J Med* 2020;383:207-217.

Ticagrelor: Reversible Mechanism of Action



Bhatt DL. *Nature Reviews Cardiology*. 2009;6:737-38.

Bentracimab: An Intravenous Monoclonal Antibody



The P2Y12 receptor is activated by adenosine diphosphate (ADP) (A).

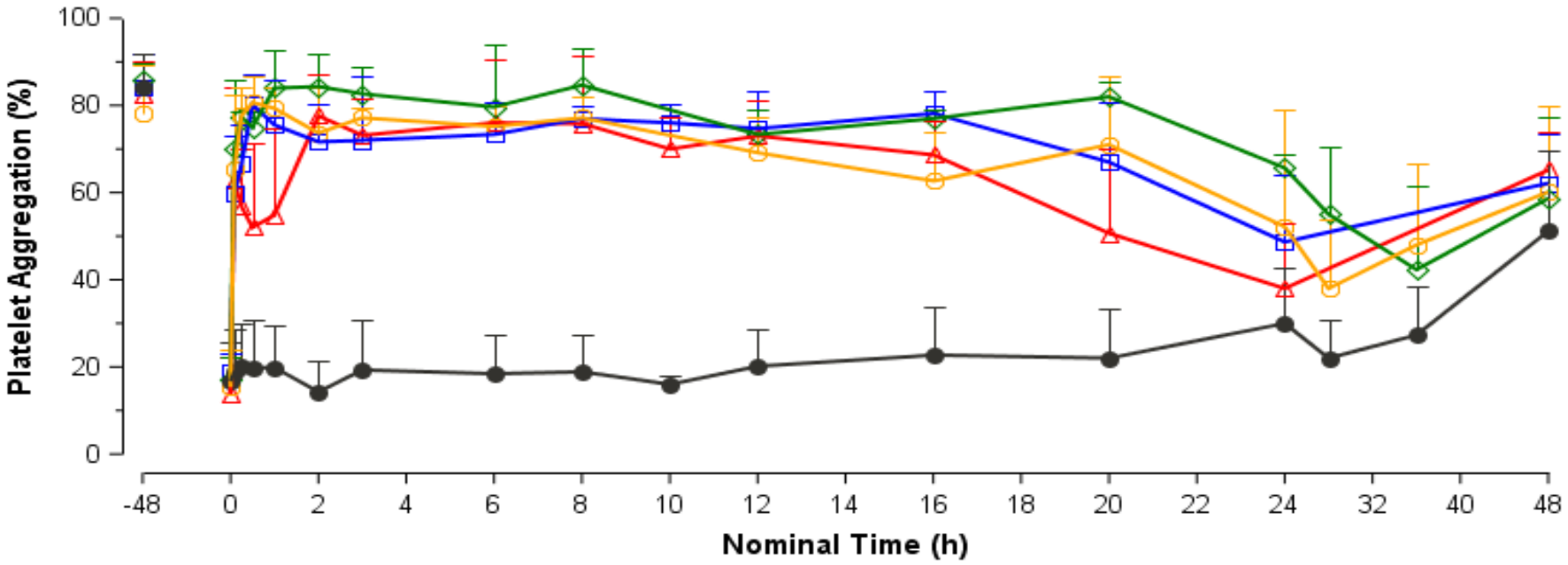
On platelets, ticagrelor reversibly binds to the P2Y12 receptor. This induces a conformational change which prevents ADP from signaling through to the P2Y12 receptor, inhibiting platelet activation (B).

Bentracimab is a recombinant human IgG1 monoclonal antibody fragment which binds to free ticagrelor with high affinity and specificity. This allows ADP to activate platelets while the bentracimab:ticagrelor complex is eliminated from the bloodstream (C and D).

Ha ACT, Bhatt DL, Rutka JT, Johnston SC, Mazer CD, Verma S. *J Am Coll Cardiol*. 2021;78:1372-1384.

Immediate Onset and Sustained Duration of Ticagrelor Reversal Using Bentracimab (formerly PB2452)

P<0.001 across all timepoints, Bonferroni adjusted

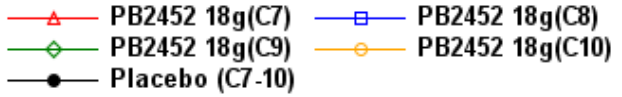


P values by timepoint for each cohort

Cohort	5min	0.25h	0.5h	1h	2h	3h	6h	8h	10h	12h	16h	20h
7	0.040	0.040	0.131	0.037	0.040	0.019	0.019	0.019	0.152	0.019	0.019	0.224
8	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.152	0.019	0.019	0.019
10	0.043	0.020	0.020	0.020	0.020	0.020	0.020	0.020	N/A	0.020	0.020	0.020

Due to the small sample size for cohort 9 (n=3), statistical testing was not performed. For Cohorts 9 and 10, no 10-hour timepoint was collected. P-values for time point 24 hours or above are not significant.

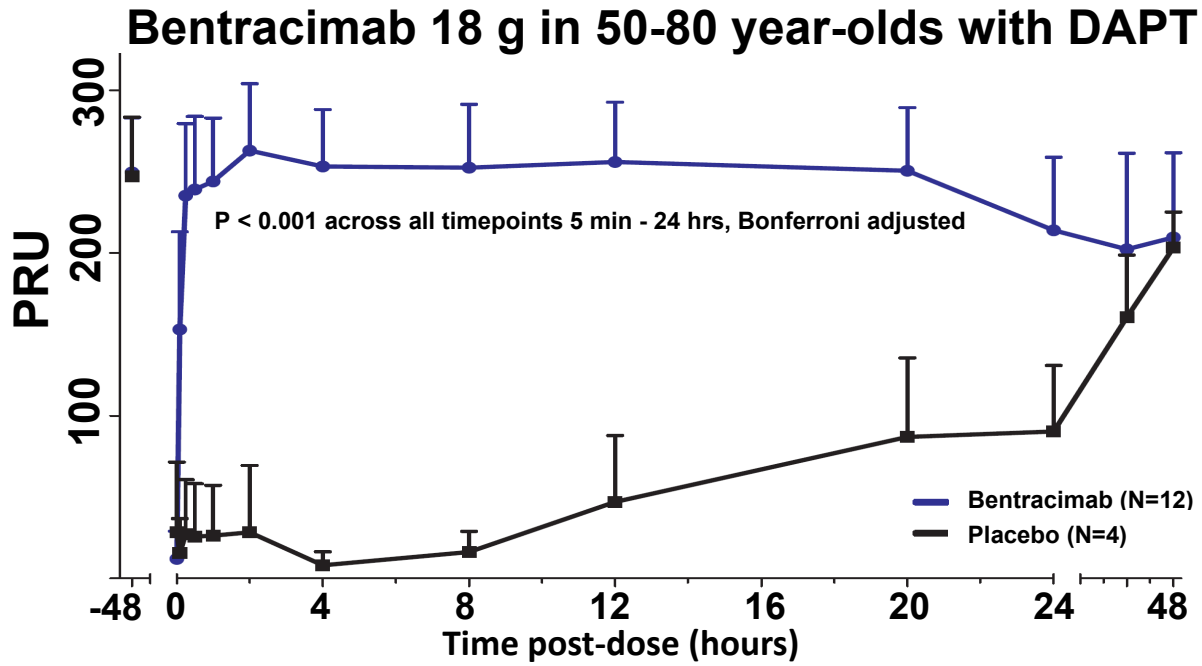
1. **Immediate and sustained ticagrelor reversal with bolus + prolonged infusion** of 18 g bentracimab.
2. Significant reversal was observed 5 minutes after initiation of bentracimab infusion.
3. Duration of reversal was infusion-time dependent, lasting 20-24 hours with a 16-hour infusion.

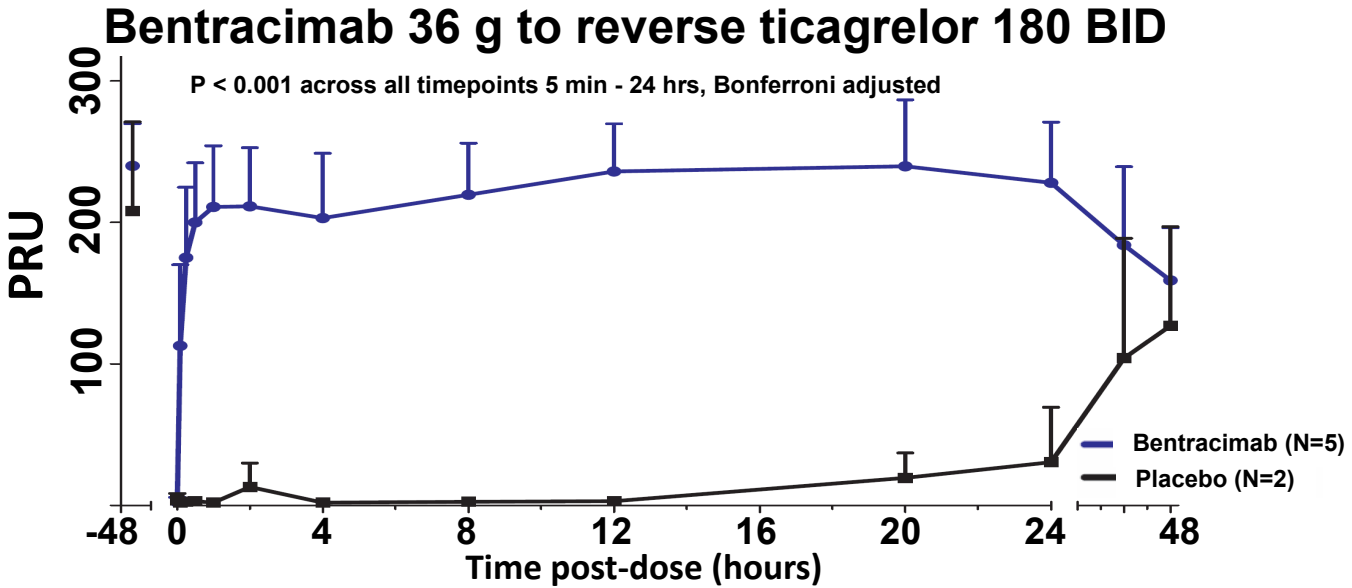


Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019; 380:1825-1833.

LTA= light transmittance aggregometry; ADP is the agonist

Bentracimab Phase 2A Data

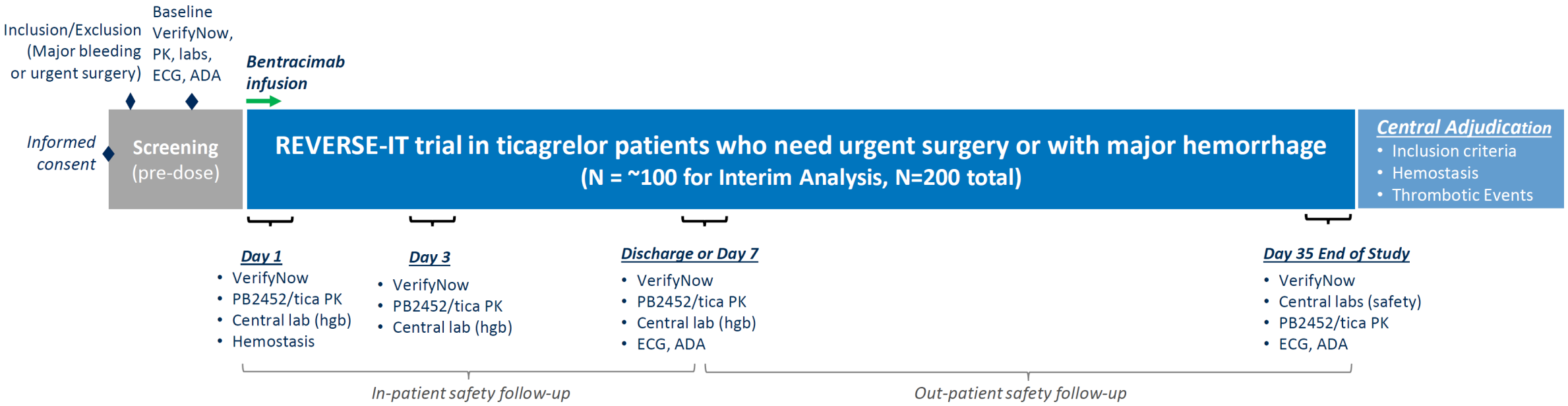




All Treatment Emergent Adverse Events

Adverse Events	PBO (N=6)	Bentracimab (N=17)
Any AE – no.	13	20
Subjects with AE – no. (%)	5 (83%)	10 (59%)
Dry mouth	1	0
Infrequent bowel movements	1	0
Nausea	1	1
Feeling hot (r)	0	2
Infusion site bruising	1	0
Infusion site erythema	1	0
Infusion site extravasation	0	1
Vessel puncture site bruise	1	4
Bronchitis	0	1
Folliculitis	0	1
Arthropod sting	1	0
Contusion	0	1
ECG T wave inversion (SAE)	0	1
Back pain	1	1
Muscle twitching	0	1
Pain in extremity	0	1
Dizziness (r)	2	1
Dyspnea (r)	0	2
Blood blister	1	0
Macule	0	1
Pruritus	0	1

REVERSE-IT: Enrollment and Study Flowchart



REVERSE-IT Study Design

Multicenter, open-label, prospective single-arm study of reversal of the antiplatelet effects of ticagrelor with **bentracimab** in **at least 200 patients** who present with **uncontrolled major or life-threatening bleeding** or who **require urgent surgery or invasive procedures**. Enrollment is ongoing in North America and Europe. Patients with use of ticagrelor within the prior 3 days who require urgent ticagrelor reversal are eligible for enrollment. **Bentracimab** was granted Breakthrough Therapy designation by the FDA and PRIME (priority medicines) designation by the European Medicines Agency, and in consultation with them, we performed this ***prespecified, interim analysis*** to support a BLA submission for an accelerated (conditional) approval.

REVERSE-IT: Endpoints

Primary Reversal Endpoint

The minimum % inhibition of PRU within 4 hours of bentracimab initiation as assessed by the Verify Now™ PRUTest™ platelet function assay

Primary Hemostasis Endpoint (Will be Centrally Adjudicated)

Achievement of effective hemostasis within 24 hours after start of PB2452 infusion assessed in each population separately and then pooled for primary endpoint analysis:

- **Uncontrolled major bleeding:** Assessed using prespecified criteria for effective hemostasis for visible and non-visible major bleeding adapted from (Connolly, 2016)
- **Urgent surgery or invasive procedure:** Assessed using prespecified criteria for effective hemostasis derived from GUSTO clinical bleeding scale (GUSTO, 1993)

REVERSE-IT Study Committees

Steering Committee

Deepak L. Bhatt MD, MPH (Chair), Dominick J. Angiolillo, MD, PhD, Stefan K. James, MD, PhD, Charles V. Pollack, Jr., MA, MD, Ph. Gabriel Steg, MD, Subodh Verma, MD, PhD, Jeffrey I. Weitz, MD

Data Safety Monitoring Board

W. Frank Peacock, MD, (Chair), Denise Ann Esserman, PhD, Sunil Rao, MD, Richard Whitlock, MD, PhD

DSMB Management: Louise Gambone

Clinical Endpoint Committee

Robert P. Giugliano MD, SM (Chair), Marc P. Bonaca, MD, MPH, John W. Eikelboom, MBBS, MS, Eli V. Gelfand, MD, Kenneth W. Mahaffey, MD, Yuri B. Pride, MD, Christian T. Ruff, MD, PhD

CEC Management: Susan Marble Gibson, Michelle Fitzpatrick

Platelet Core Lab

Lisa K. Jennings, PhD, Ben Curry, PhD

REVERSE-IT Investigators

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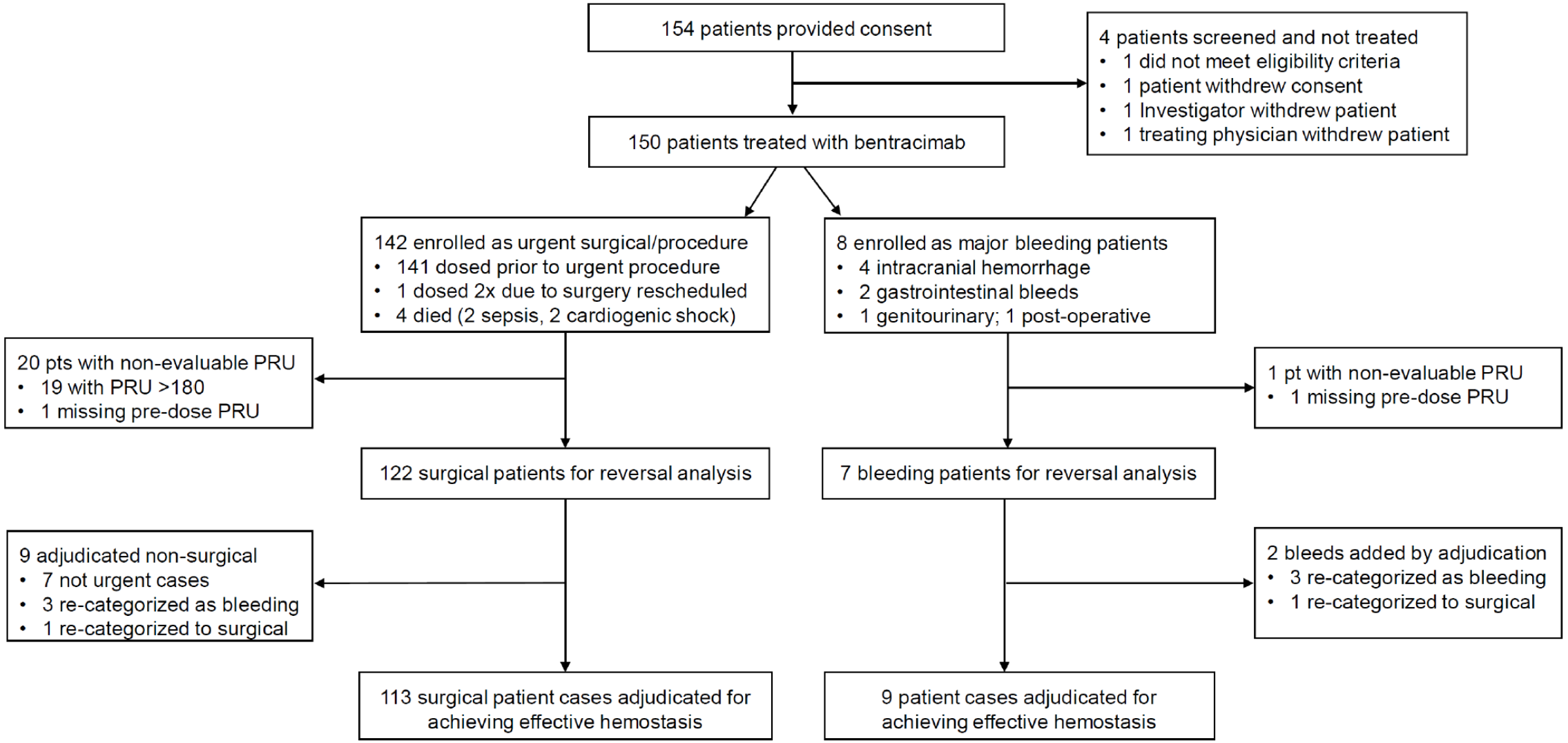
Mentor Ahmeti, MD, Denis Angoulvant, MD, PhD, Craig Brown, MD, Warren Cantor, MD, Michael Charles, MD, Marc Claeys, MD, PhD, Francesco Franchi, MD, Alex Gregory, MD, Zafir Hawa, MD, Michael Heffernan, MD, John Kotter, MD, Gilles Lemesle, MD, PhD, David Mazer, MD, Shamir Mehta, MD, Marc Ruel, MD, Tarit Saha, MD, Jean-Francois Tanguay, MD, Jurrien M. Ten Berg, MD, PhD, Marco Valgimigli, MD, PhD, Sam Van Boxstael, MD, Philippe Vanduynhoven, MD, Pierre Voisine, MD, Terry Yau, MD

REVERSE-IT: Enrollment and Study Flowchart

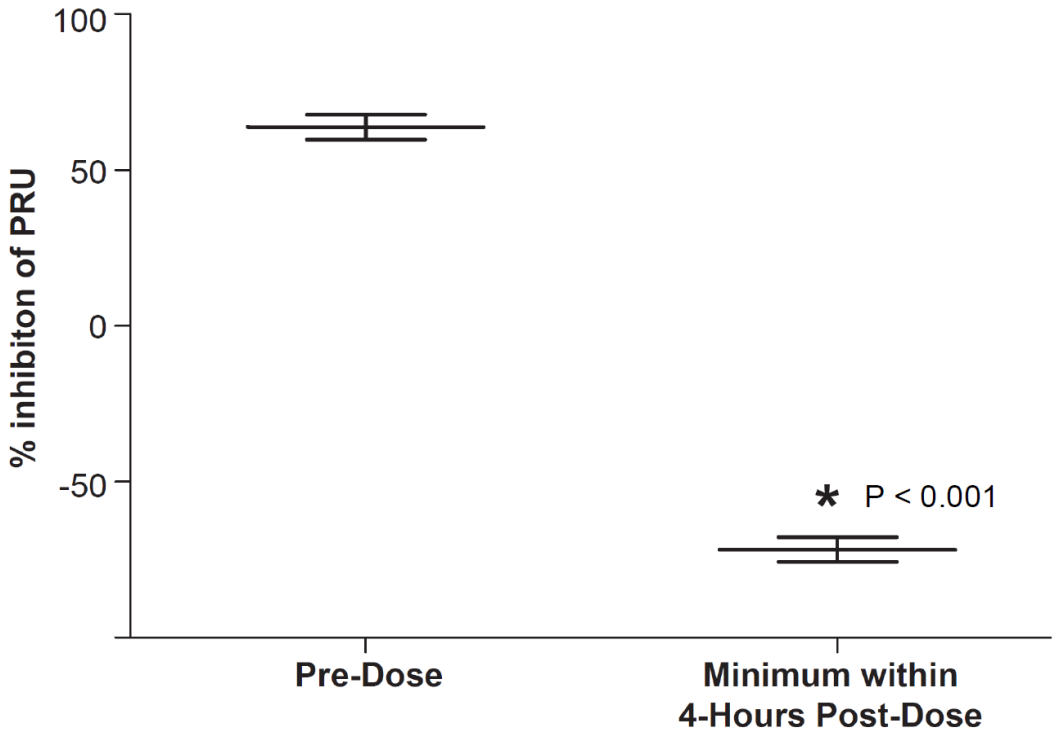


REVERSE-IT: Baseline Characteristics

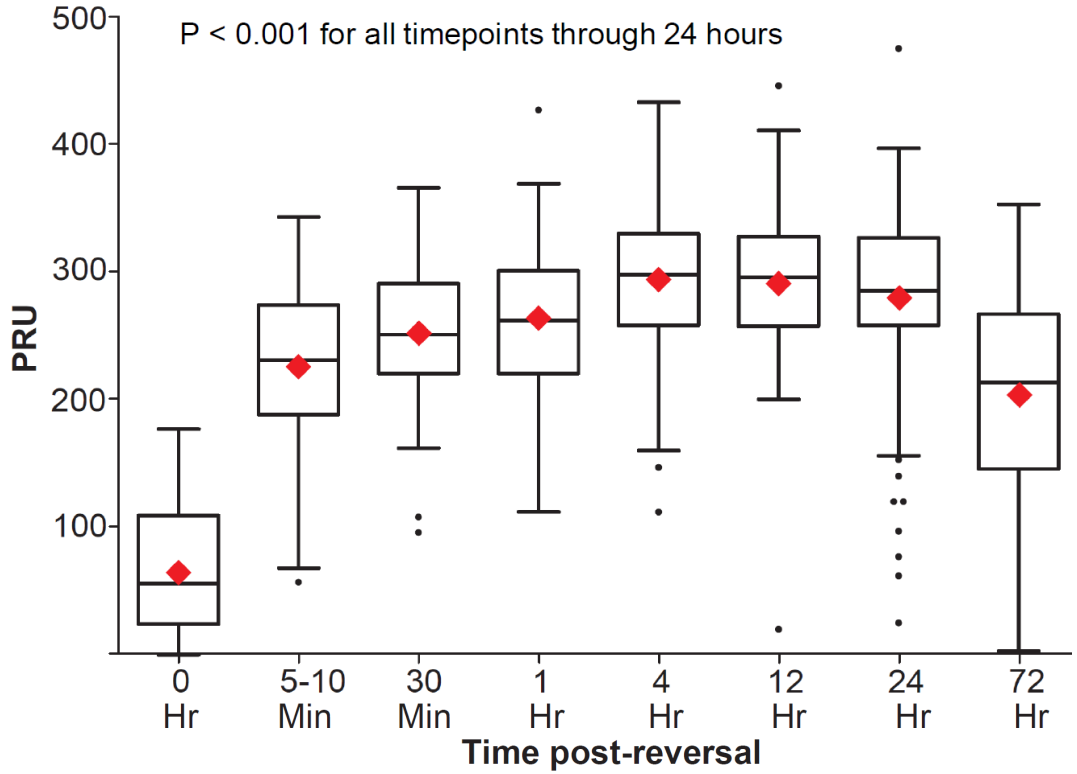
Characteristic	Surgical (N=142)	Bleeding (N=8)	Total (N=150)
Age (years), Mean (SD)	64.8 (10.46)	67.0 (13.40)	65.0 (10.59)
Sex, n (%)			
Male	112 (78.9)	4 (50.0)	116 (77.3)
Female	30 (21.1)	4 (50.0)	34 (22.8)
Weight (kg), Mean (SD)	85.2 (19.33)	76.9 (29.72)	84.8 (19.87)
Height (cm), Mean (SD)	170 (8.62)	169 (11.69)	171 (8.75)
BMI (kg/m^2), Mean (SD)	29.1 (6.21)	27.8 (11.46)	29.1 (6.49)
Ethnicity, n (%)			
Hispanic or Latino	1 (0.7)	2 (25.0)	3 (2.0)
Not Hispanic or Latino	141 (99.3)	6 (75.0)	147 (98.0)
Race, n (%)			
White	118 (83.1)	7 (87.5)	125 (83.3)
Black or African American	5 (3.5)	1 (12.5)	6 (4.0)
Asian	16 (11.3)	0 (0)	16 (10.7)
American Indian or Alaskan	1 (0.7)	0 (0)	1 (0.7)
Other	2 (1.4)	0 (0)	2 (1.3)
Hypertension	114 (80.3)	6 (75.0)	120 (80.0)
Diabetes	57 (40.1)	2 (25.0)	59 (39.3)
Myocardial infarction	118 (83.1)	4 (50.0)	122 (81.3)
Baseline eGFR (MDRD)			
eGFR < 60, n (%)	32 (22.5)	0 (0)	32 (21.3)
Time from last ticagrelor, n (%)			
0-1 days	100 (70.4)	7 (87.5)	107 (71.3)
2 days	29 (20.4)	1 (12.5)	30 (20.0)
3 days	13 (9.2)	0 (0)	13 (8.7)

REVERSE-IT: Platelet Function Tests

Percent Inhibition of PRU



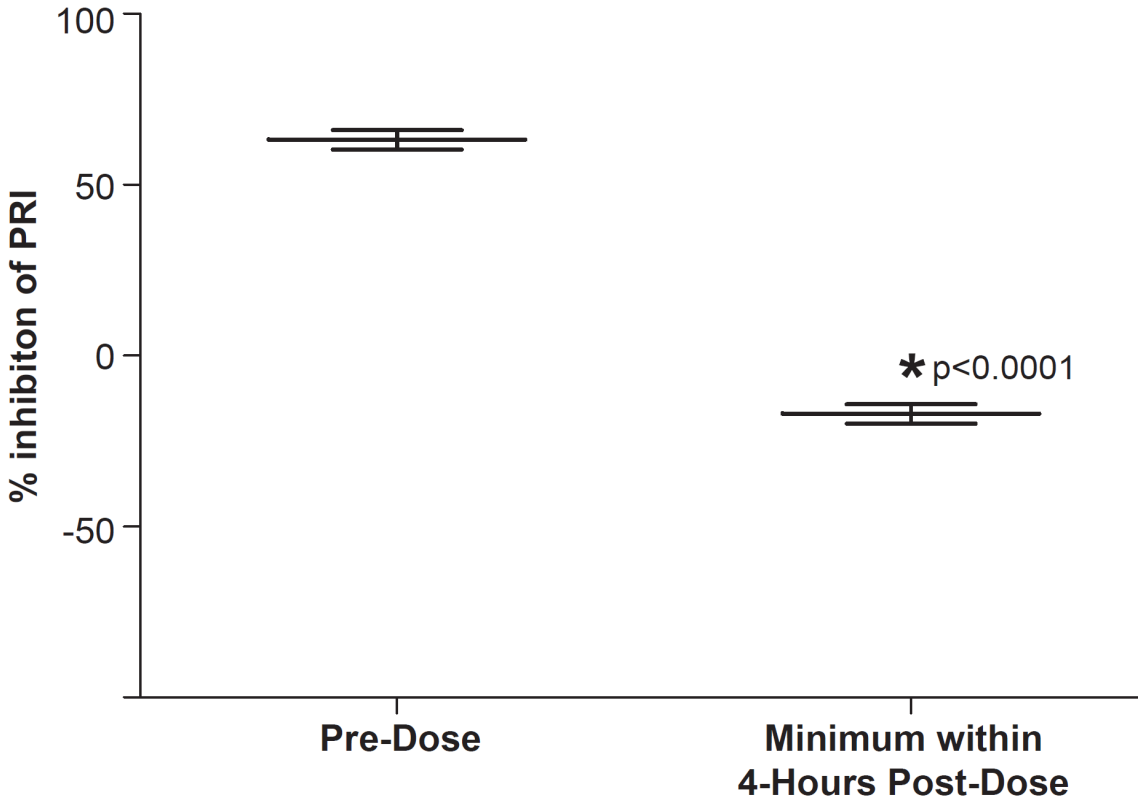
PRU Analysis of Reversal



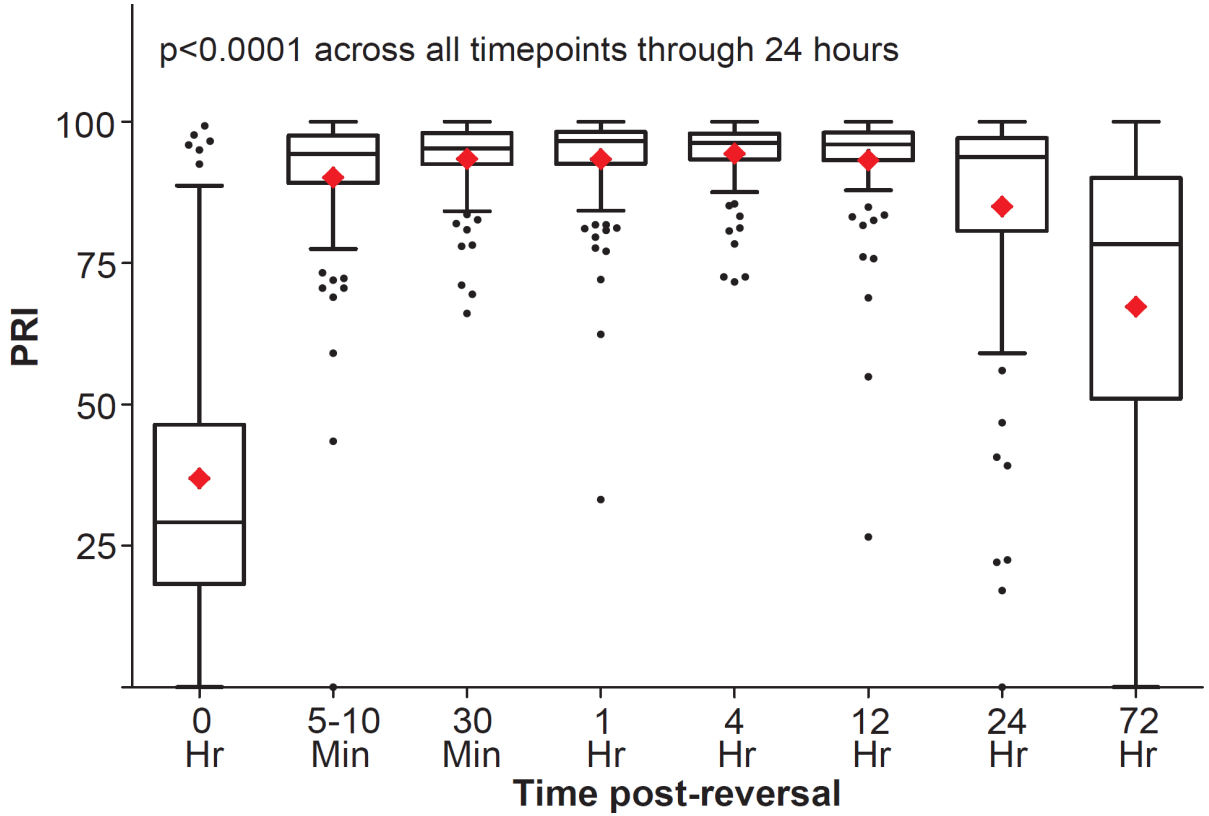
Ticagrelor Reversal with VerifyNow PRU. Ticagrelor reversal is shown as a reduction in % inhibition of PRU or PRI and as an increase in PRU or platelet reactivity index at multiple timepoints post-treatment. Shown is the comparison of % inhibition of PRU pre-treatment and the minimum % inhibition of PRU within 4 hours of initiation of bentracimab infusion (left). Onset and duration of ticagrelor reversal in bentracimab-treated patients observed as an increase in PRU with P value at each timepoint Bonferroni adjusted (right).

REVERSE-IT: Platelet Function Tests

Percent Inhibition of PRI



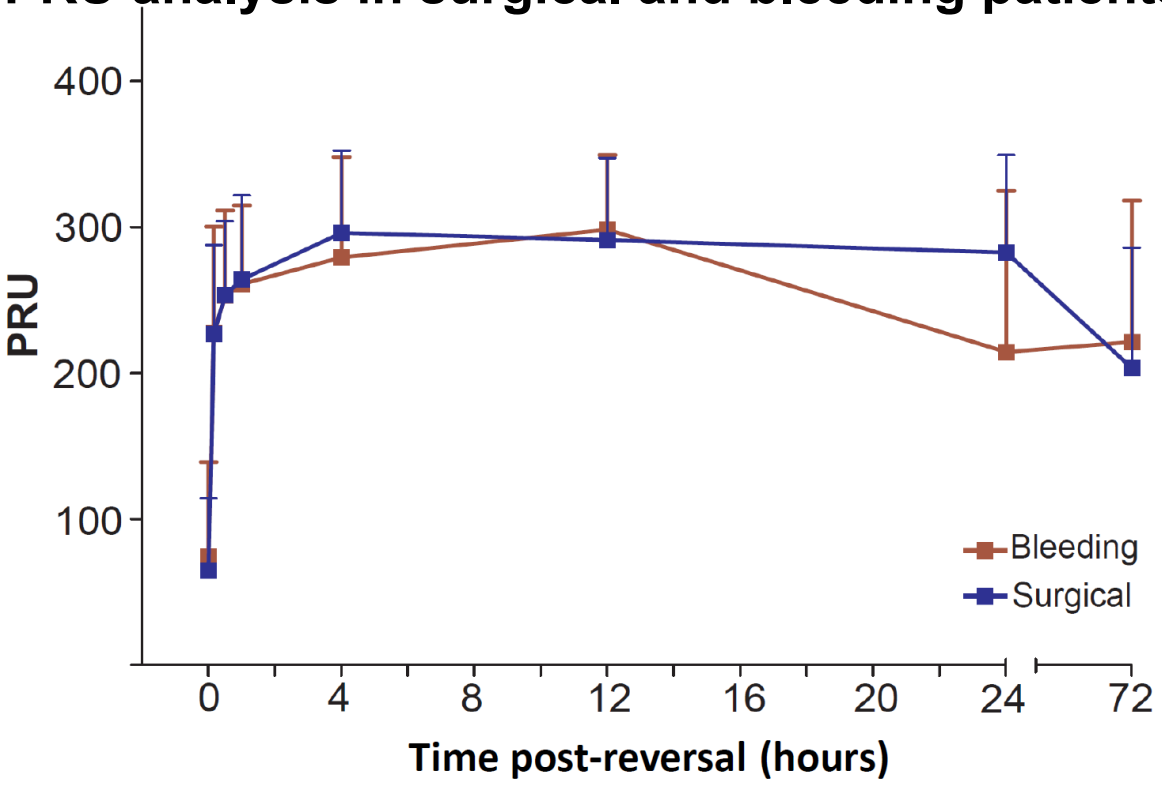
PRI analysis of Reversal



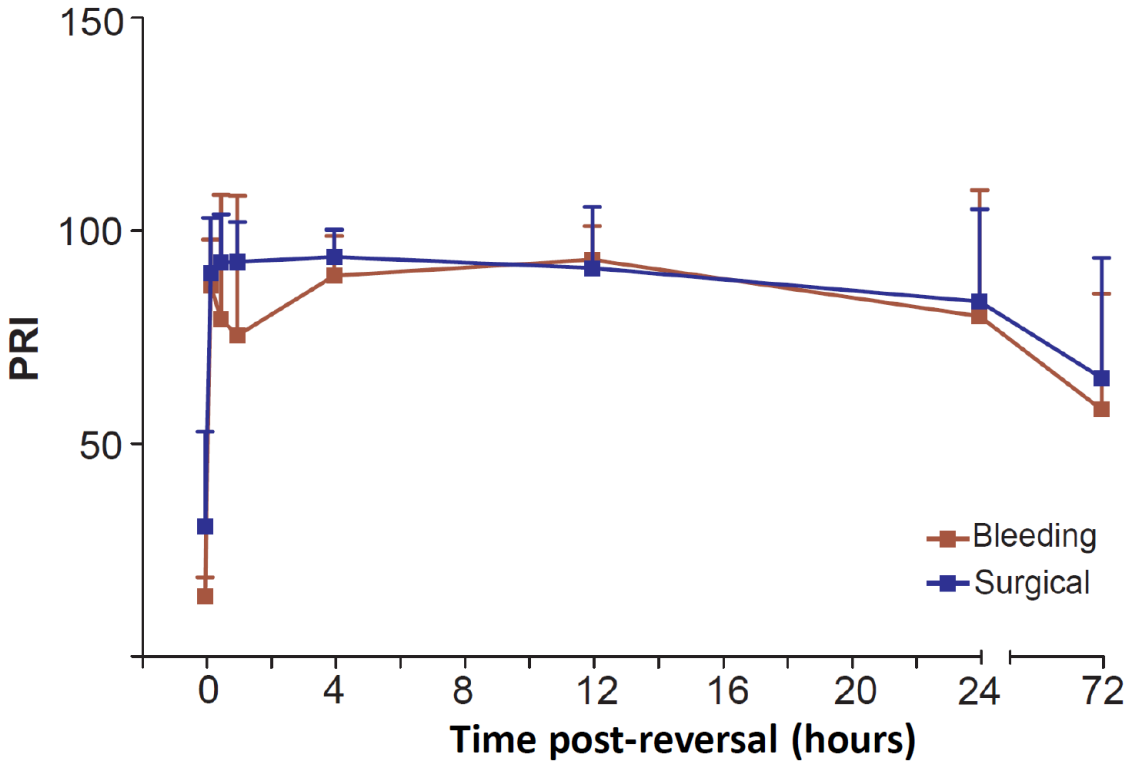
Ticagrelor Reversal with VASP platelet reactivity index (PRI). Comparison of % inhibition of platelet reactivity index pre-treatment and the minimum % inhibition of platelet reactivity index within 4 hours of initiation of bentracimab infusion (left). The onset and duration of ticagrelor reversal in bentracimab-treated patients observed as an increase in platelet reactivity index with P value at each timepoint Bonferroni adjusted (right).

REVERSE-IT: Reversal in Surgical and Bleeding Pts

PRU analysis in surgical and bleeding patients



PRI analysis in surgical and bleeding patients

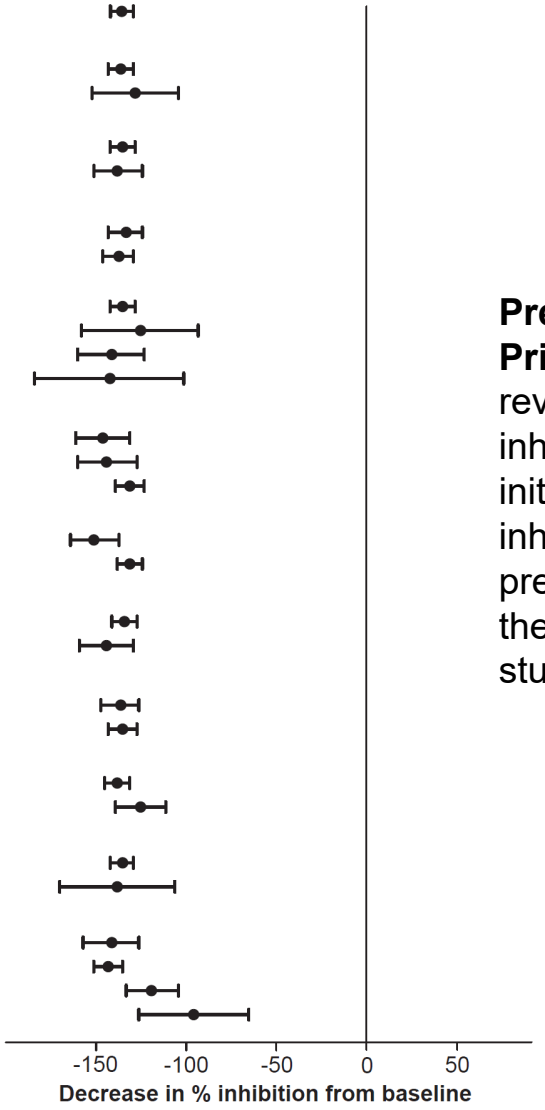


Ticagrelor Reversal in Bleeding and Surgical Patients. Multiple platelet function assays were used to measure extent of ticagrelor reversal in bleeding and surgical patients. Shown is platelet aggregation pre-treatment and at multiple timepoints post initiation of bentracimab in bleeding patients compared to surgical patients as measured by VerifyNow P2Y12 assay (left). The VASP PRI assay was used to assess ticagrelor's suppression of P2Y12 receptor signaling pre-treatment and at multiple timepoint post-initiation of bentracimab in bleeding vs. surgical patients (right).

REVERSE-IT: Platelet Function Tests *Subgroups*

Forest Plot for % Inhibition of PRU

Subgroup	n (%)	Difference in % inhibition Mean (95%CI)	Statistical Significance (p)
Overall	129 (100)	-135 (-142, -129)	<0.0001
Patient Population			
Surgery	120 (93)	-136 (-143, -129)	<0.0001
Bleeding	9 (7)	-128 (-152, -104)	<0.0001
Sex			
Male	101 (78.3)	-135 (-142, -128)	<0.0001
Female	28 (21.7)	-138 (-151, -124)	<0.0001
Age			
< 65 years	58 (45)	-133 (-143, -124)	<0.0001
≥ 65 years	71 (55)	-137 (-146, -129)	<0.0001
Race			
White	106 (82.2)	-135 (-142, -128)	<0.0001
Black	5 (3.9)	-125 (-158, -93.0)	<0.0001
Asian	15 (11.6)	-141 (-160, -123)	<0.0001
Other	3 (2.3)	-142 (-184, -101)	<0.0001
Region			
USA	23 (17.8)	-146 (-161, -131)	<0.0001
Europe	18 (14)	-144 (-160, -127)	<0.0001
Canada	88 (68.2)	-131 (-139, -123)	<0.0001
Renal Function			
GFR < 60	28 (21.7)	-151 (-164, -137)	<0.0001
GFR ≥ 60	101 (78.3)	-131 (-138, -124)	<0.0001
Myocardial Infarction			
Yes	106 (82.2)	-134 (-141, -127)	<0.0001
No	23 (17.8)	-144 (-159, -129)	<0.0001
Diabetes			
Yes	50 (38.8)	-136 (-147, -126)	<0.0001
No	79 (61.2)	-135 (-143, -127)	<0.0001
Hypertension			
Yes	102 (79.1)	-138 (-145, -131)	<0.0001
No	27 (20.9)	-125 (-139, -111)	<0.0001
CYP3A Inhibitor			
None/Mild	124 (96.1)	-135 (-142, -129)	<0.0001
Moderate/Strong	5 (3.9)	-138 (-170, -106)	<0.0001
Time from last Ticagrelor			
0 Days	19 (14.7)	-141 (-157, -126)	<0.0001
1 Day	74 (57.4)	-143 (-151, -135)	<0.0001
2 Days	23 (17.8)	-119 (-133, -104)	<0.0001
3+ Days	5 (3.9)	-95.4 (-126, -64.8)	<0.0001



Prespecified Subgroup Analyses of the Primary Reversal Endpoint. The primary reversal endpoint was the minimum % inhibition of PRU within 4 hours of study drug initiation compared to pre-treatment % inhibition of PRU. Shown is a Forest plot of the pretreatment % inhibition of PRU compared to the minimum %inhibition within 4 hours of study drug in pre-specified subgroups.

Enrollment of Urgent Surgical and Major Bleeding Patients in REVERSE-IT

Enrolled Urgent Surgical and Major Bleeding Patients

Patient Type	n (%)
Total Surgical Patients	142
Cardiac Surgery	131 (92)
Emergency CABG	27 (19)
Urgent CABG	103 (72)
Valve replacement	5 (3.5)
Aortic dissection repair	2 (1.4)
General (Abdominal) Surgery	3 (0.3)
Orthopedic Surgery	3 (0.3)
Invasive endoscopic	3 (0.3)
Neurosurgery	2 (1.4)
Total Bleeding Patients	8
Intracranial Hemorrhage	4 (50)
Gastrointestinal	2 (25)
Post-Operative	1 (12.5)
Urological	1 (12.5)

CABG, coronary artery bypass graft surgery. Emergency CABG was defined *post hoc* as CABG performed within 24 hours of ticagrelor 180 mg pretreatment. Urgent CABG was all other CABG performed in REVERSE-IT. Duration of ticagrelor washout prior to CABG was based on clinical judgement. The study protocol did not require attempted washout prior to enrollment.

REVERSE-IT: Adjudicated Surgical Hemostasis

Adjudicated and Investigator-Reported Surgical Outcomes

Hemostasis in Surgical Patients	**n (%)**
Adjudicated achieved hemostasis (N=113)	113 (100.0)
GUSTO Mild	75 (66.4)
GUSTO Moderate	38 (33.6)
GUSTO Severe	0 (0)
Investigator-reported achieved hemostasis (N=142)	135 (95.1)
Normal or mildly abnormal bleeding	110 (77.5)
Moderately abnormal	25 (17.6)
Severely abnormal or unknown	7 (4.93)
Blood Product Transfusions	**n (%)**
Total blood transfusions (pRBCs or whole blood)	56 (39.04)
Blood transfusions for bleeding event	10 (7.04)
Total platelets transfusions	19 (13.4)
Platelet transfusions for bleeding event	6 (4.22)
Other Surgical Outcomes	
Restarted $P2Y_{12}$ inhibition, n (%)	111 (74%)
Time to restart (median), days (min, max)	2 (0, 22)
Total mortality, n (%)	4 (2.8)

pRBC, packed red blood cells. Investigators were required to specify in case report forms whether allogeneic blood and platelet products were transfused for bleeding events or other routine perioperative use. Total transfusions and transfusions for bleeding events are shown above.

REVERSE-IT: Adjudicated Bleeding Hemostasis

Adjudicated and Investigator-Reported Bleeding Outcomes

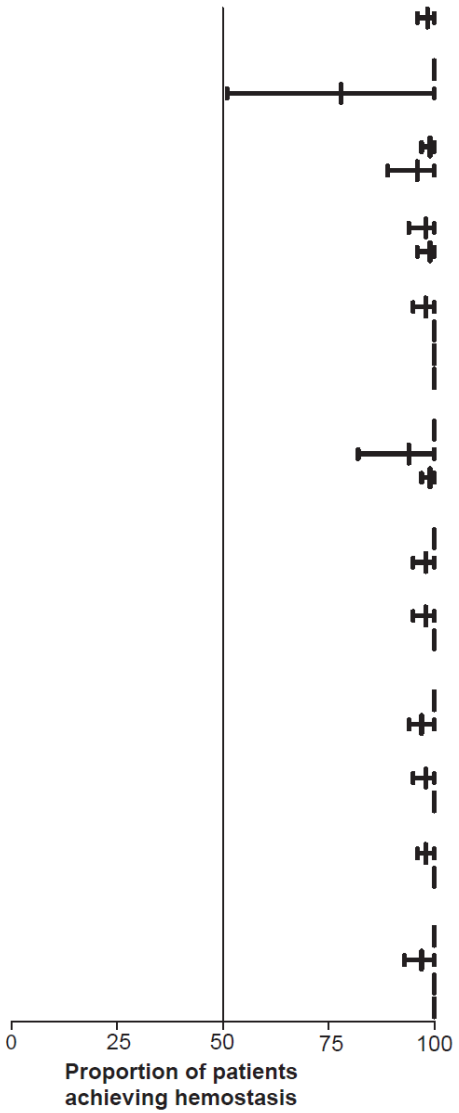
Hemostasis in Bleeding Patients	**n (%)**
Adjudicated achieved hemostasis (N=9)	7 (77.8)
Excellent hemostasis	6 (66.7)
Good hemostasis	1 (11.1)
Poor hemostasis	1 (11.1)
Unable to determine	1 (11.1)
Investigator-reported achieved hemostasis (N=8)	7 (87.5)
Median time to hemostasis, hrs (min, max)	23 (112, 7)
Blood Product Transfusions	**n (%)**
Total blood transfusions (pRBCs or whole blood)	5 (62.5)
Blood transfusions for bleeding event	5 (62.5)
Total platelet transfusions	2 (25.0)
Platelet transfusions for bleeding event	1 (12.5)
Other Outcomes in Bleeding Patients	
Restarted $P2Y_{12}$ inhibition, n (%)	5 (62.5)
Time to restart (median), days (min, max)	5 (0, 8)
Total mortality, n (%)	0 (0.0)

REVERSE-IT: Adjudicated Hemostasis *Subgroups*

Forest Plot for Effective Hemostasis (Adjudicated)

Subgroup	n/N	Proportion of patients achieving hemostasis	Statistical Significance (p)
Overall	120/122	99 (96, 100)	<0.0001
Patient Population			
Surgery	113/113	100 (100,100)	<0.0001
Bleeding	7/9	78 (51, 100)	0.0956
Sex			
Male	95/96	99 (97, 100)	<0.0001
Female	25/26	96 (89, 100)	<0.0001
Age			
< 65 years	51/52	98 (94, 100)	<0.0001
≥ 65 years	69/70	99 (96, 100)	<0.0001
Race			
White	99/101	98 (95, 100)	<0.0001
Black	4/4	100 (100,100)	0.0455
Asian	15/15	100 (100,100)	0.0001
Other	2/2	100 (100,100)	0.1573
Region			
USA	20/20	100 (100,100)	<0.0001
Europe	15/16	94 (82, 100)	0.0005
Canada	85/86	99 (97, 100)	<0.0001
Renal Function			
GFR < 60	30/30	100 (100,100)	<0.0001
GFR ≥ 60	90/92	98 (95, 100)	<0.0001
Myocardial Infarction			
Yes	99/101	98 (95, 100)	<0.0001
No	21/21	100 (100,100)	<0.0001
Diabetes			
Yes	48/48	100 (100,100)	<0.0001
No	72/74	97 (94, 100)	<0.0001
Hypertension			
Yes	94/96	98 (95, 100)	<0.0001
No	26/26	100 (100,100)	<0.0001
CYP3A Inhibitor			
None/Mild	115/117	98 (96, 100)	<0.0001
Moderate/Strong	5/5	100 (100,100)	0.0253
Time from last Ticagrelor			
0 Days	19/19	100 (100,100)	<0.0001
1 Day	67/69	97 (93, 100)	<0.0001
2 Days	22/22	100 (100,100)	<0.0001
3+ Days	4/4	100 (100,100)	0.0455

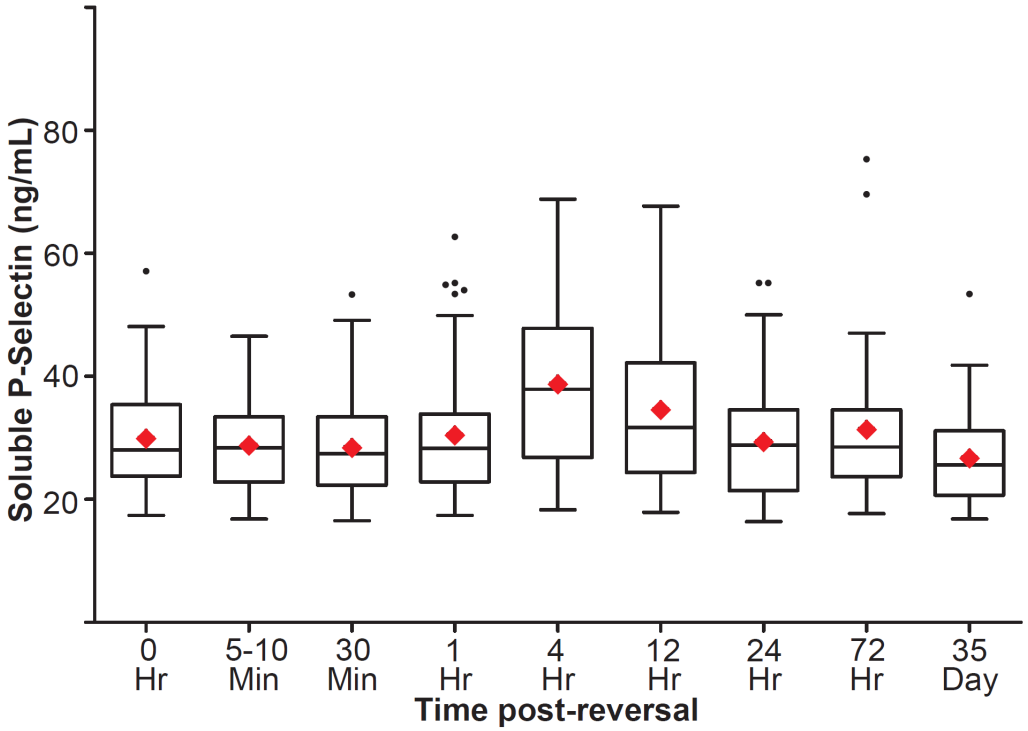
n represents the number of subjects successfully achieving hemostasis
N represents the total number of subjects in the category
Note: Confidence intervals are bounded at 100%



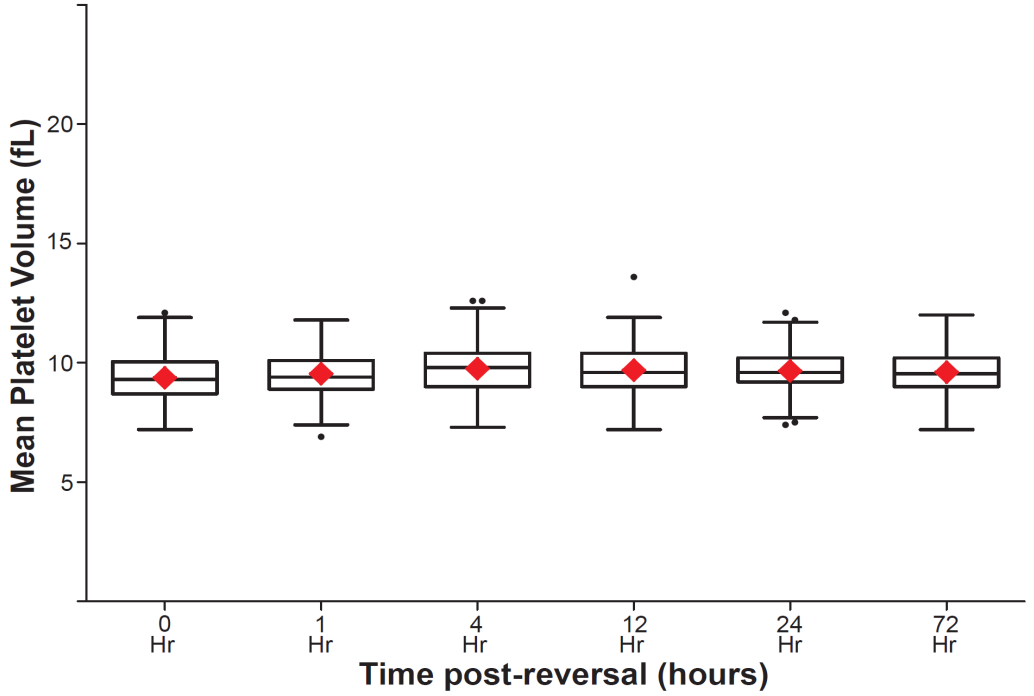
Prespecified Subgroup Analyses of the Primary Hemostasis Endpoint. The primary hemostasis endpoint was the proportion of patients adjudicated to have achieved effective hemostasis compared to 50% expected by the null hypothesis. Shown is a Forest plot of the proportion of patients with effective hemostasis within 24 hours of initiation of bentracimab infusion in pre-specified subgroups

REVERSE-IT: No Platelet Rebound Activity

P-selectin in surgical and bleeding patients



Mean platelet volume in surgical and bleeding patients



Effect of Bentracimab Treatment on P-Selectin and Mean Platelet Volume (MPV). Soluble P-selectin and MPV were measured pre-dose and at multiple timepoints post-initiation of bentracimab treatment to assess for a potentially prothrombotic rebound increase in platelet reactivity post-reversal. Shown are the soluble P-selectin levels in surgical and bleeding patients treated with bentracimab (left). MPV was measured in surgical and bleeding patients treated with bentracimab (right).

REVERSE-IT: Adjudicated Thrombotic Events

Adjudicated Thrombotic Events Occurring Post-Reversal

Patient Type	Type of Event	Days from Bentracimab and Surgery	P2Y12 restarted before event	Related to bentracimab
51 yr old man, s/p CABG	Myocardial infarction	7	Yes	No
78 yr old woman, s/p CABG	Transient ischemic attack	2	Yes	No
70 yr old man, s/p CABG	Lacunar stroke	1	No	No
58 yr old man, s/p CABG	Anterior, inferior STEMI with total graft occlusion	1	No	No
69 yr old man, s/p CABG, intraortic balloon pump, and thrombectomy	RLE arterial thromboembolism	1	No	No
73 yr of woman, s/p CABG	Acute ischemic stroke	5	No	No
44 yr old male, s/p CABG	Acute coronary syndrome with graft failure	29	Yes	No
47 yr old man, s/p CABG +aortic dissection repair	Acute ischemic right leg immediately post-op	1	No	No

Limitations

- There was no control arm, as it was felt to be challenging to randomize to a placebo (as with the NOAC reversal trials).
- The majority of surgical patients underwent cardiac surgery, though no reason to think the results don't apply to other surgeries and invasive procedures.
- The number of patients with bleeding in this prespecified interim analysis was low, though surgery is an excellent model of bleeding (and the bleeding subgroup showed statistically significant benefits).
  - Enrollment of additional patients with bleeding is ongoing.

Conclusion

- Using the VerifyNow and VASP assays in ticagrelor-treated patients undergoing invasive procedures or with major bleeding, **bentracimab**, a specific reversal agent for ticagrelor, provided **immediate and sustained reversal of ticagrelor's antiplatelet effects.**
- Rates of **effective hemostasis** were adjudicated as good or excellent in >90% of cases, with no drug-related serious adverse events or allergic or infusion-related reactions .
- The benefits were **consistent in all prespecified subgroups**, including those undergoing surgery and with major bleeding.
- **Bentracimab** appears to be a very promising option for **ticagrelor reversal**.

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Deepak L. Bhatt, MD, MPH, Charles V. Pollack, Jr., MD, C. David Mazer, MD, Dominick J. Angiolillo, MD, PhD, Ph. Gabriel Steg, MD, Stefan K. James, MD, PhD, Jeffrey I. Weitz, MD, Rohit Ramnath, PhD, Susan E. Arnold, PhD, Michael C. Mays, BS, Bret R. Umstead, MS, Barbara White, MD, Lisa L. Hickey, MS, Lisa K. Jennings, PhD, Benjamin J. Curry, PhD, John S. Lee MD, PhD, Subodh Verma, MD, PhD, on Behalf of the REVERSE-IT Investigators

BRIGHAM AND WOMEN'S HOSPITAL

Heart & Vascular Center

Thank You!

Deepak L. Bhatt, MD, MPH
Executive Director,
Interventional Cardiovascular Programs,
BWH Heart & Vascular Center;
Professor of Medicine,
Harvard Medical School
Email: DLBhattMD@post.Harvard.edu
Twitter: @DLBhattMD

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